Cardiovascular disease: revascularisation

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GUIDELINES

1. **In patients with chronic kidney disease 2 and 3 with increasing angina, angina at rest or who have suspicion of a myocardial infarction in the previous 48 hours, with >70% coronary artery stenoses, acute revascularisation with coronary artery bypass graft or percutaneous intervention results in a reduction in the incidence of myocardial infarction and death compared with conservative treatment. (Level II)**

2. **The use of drug eluting stents is associated with a lower re-stenosis rate than the use of bare metal stents in patients with chronic kidney disease (Level II)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

1. **Revascularisation of coronary arteries with coronary artery bypass graft (CABG) and percutaneous intervention (PCI) is associated with greater mortality in patients with chronic kidney disease (CKD) compared with the general population.**
2. **Revascularisation of coronary arteries with CABG and PCI is associated with greater mortality in dialysis patients compared with the general population.**
3. **Revascularisation of coronary arteries in transplant patients is associated with a low risk of returning to dialysis.**
4. **In patients with coronary artery disease (CAD), CABG is associated with improved all-cause and cardiac survival compared with angioplasty in dialysis patients.**
5. **Coronary artery stenting (CAS) is associated with improved all-cause and cardiac survival compared with angioplasty in dialysis patients who do not have diabetes mellitus.**
6. **In patients with CAD and renal transplants, CABG with internal mammary artery grafting is associated with a reduced risk of cardiac death or myocardial infarction (MI) compared with percutaneous intervention.**

Implementation and audit

At this stage, it is difficult to implement or audit these guidelines as they are largely involving patients with less severe degrees of kidney disease and often these patients will not be referred to nephrology services. Registries of all patients with CKD undergoing coronary artery revascularization will assist with enlightening the nephrology and cardiology sectors about outcomes after revascularision.

Background

Cardiovascular disease is the leading cause of death in patients with end stage renal failure. The risk of cardiovascular death is significantly reduced in the renal transplant population compared with those on dialysis, but is still significantly greater than that of the general population [1]. In addition, the risk of cardiac death and major cardiac events is greater in those with CKD than those with normal renal function [2,3].

Revascularisation of coronary artery stenoses has been extensively studied in the general population and guidelines for the management of both unstable [4] and stable [5] CAD have been generated using evidence from randomised controlled trials. Clear comparisons of CABG, PCI and Stenting have been made in the general population however in most trials, patients with renal impairment have been excluded.

The aim of this guideline is to review the literature and assess the benefits and harms of revascularisation of CAD in patients with CKD, including the dialysis and transplant populations. The literature examining revascularisation was examined both in unstable and stable CAD.

Search strategy

Databases searched: MeSH terms and text words for chronic kidney disease, end-stage kidney disease and renal replacement therapy were combined with MeSH terms and text words for cardiovascular disease and then combined with MeSH terms and text words for revascularisation and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1950 - September Week 1, 2007). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 7 September 2007.

What is the evidence?

Randomised controlled trials (RCT): Unfortunately there are few RCT examining outcomes after revascularisation. Much of the RCT data is taken from post-hoc analyses of RCT from the general population where patients with CKD were identified and analysed.

Revascularisation compared with medical therapy: stable or asymptomatic CAD

Normal population

There are a number of studies in the normal population comparing revascularisation with medical therapy. The first large scale RCT was the Veteran Affairs (VA) Co-operative Study of Coronary Artery Bypass Surgery [6]. While short-term survival in patients with stable angina and Left Main Stem disease was superior in the revascularisation group, this benefit diminished over time and by 18 years, there was no benefit in survival or the incidence of MI in those who underwent CABG, compared with those treated with medical therapy.

CKD population

There is only one RCT comparing revascularisation with medical treatment in patients with CKD [7]. All patients had insulin dependent diabetes mellitus (mainly Type I) and underwent coronary angiography as part of the assessment for transplantation listing. Twenty-six patients were randomised to medical treatment (Calcium Channel Blocker (CCB) + aspirin) or revascularisation. The study was powered to enrol 162 patients to detect a 10% improvement with revascularisation. Ten patients in the medically treated group and 2 in the revascularisation group reached cardiac

endpoints (unstable angina, MI, cardiac death) in a median time of 8.4 months. Three medically treated patients died of MI compared with no deaths from MI in the revascularisation group.

The study was terminated 30 months after recruitment commenced because of both slow patient recruitment and excess events in the medically treated group after an interim analysis at 24 months. The paper does not comment on the severity of CKD nor on the proportion of patients already on dialysis, however, presumably patients had severe CKD as transplantation was being considered. Ten patients (5 in each group) had dialysis initiated during the course of the study.

This study was hampered by low recruitment, low use of beta blockers, the use of short acting CCB and variable aspirin use. In addition, the follow-up was short. The authors conclude that a larger study is needed.

There are no other studies in the renal population, however, a large RCT was performed in patients scheduled for vascular surgery. This group of patients is at very high risk for cardiac events [8]. A total of 510 patients were randomised to pre-operative coronary artery revascularisation (CABG or PCI) or conservative medical therapy. Patients randomised to revascularisation underwent CABG or PCI prior to their vascular surgery. There was no survival benefit in revascularisation compared with no revascularisation for any subgroup of patients with 6 years of follow-up. Incidentally, there was no difference in the use of statins, beta-blockers, aspirin or ACE Inhibitors between the two groups.

Revascularisation compared with medical therapy: unstable CAD

Normal population

Acute revascularisation of unstable CAD has been examined in a RCT in the Fast Revascularisation in Instability in Coronary Disease Trial (FRISC II trial) [9]. This showed a reduction in the combined endpoint of death or MI in the revascularisation group compared with those who were managed medically. Patients in each group were also randomised to dalteparin or placebo. Revascularisation was performed using CABG or PCI as determined by the local investigators (see Fig. 1).

CKD population

Patients in the FRISC II Trial were then analysed in tertiles of creatinine clearance estimated using the Cockcroft-Gault (CG) formula [10]. There were 842 patients with a creatinine clearance of less than 69ml/min. A reduced creatinine clearance was associated with a higher rate of the combined end point of death or MI. The incidence of death and or MI at 2 years in patients with a creatinine clearance of less than 69 mL/min was significantly reduced in those treated with early invasive intervention compared with those managed non-invasively (14.6% invasive group compared with 22.4% non-invasive group; P = 0.003). Indeed the benefit of early invasive therapy was restricted to patients with a creatinine clearance of less than 90mL/min. There were no patients in this study with CKD 5 and only 6 patients (0.2%) with CKD 4.

Another study examined patients with renal impairment from the TACTICS-TIMI 18 trial where patients with a Non ST Elevation acute coronary syndrome were treated with heparin, aspirin and tirofiban and randomised to early invasive treatment compared with a selectively invasive arm in which coronary angiography was reserved for recurrent instability or failed provocative studies for myocardial ischemia. In this trial, patients with a creatinine >2,5mg/dL were excluded. The sub-study [11] analysed renal function by creatinine clearance using a Cockcroft Gault formula. This study also showed that decreasing renal function is a risk factor for adverse outcomes. Routine invasive treatment was found to reduce the endpoints of death, acute MI and rehospitalisation for acute coronary syndrome at 30 days and 6 months in all categories of creatinine clearance. In this study, there were only 28 patients with CKD 4 and 5.

Revascularisation: coronary artery surgery compared with percutaneous intervention

Normal population

The Bypass Angioplasty Revascularisation Investigation (BARI) Trial randomised patients with multi-vessel CAD requiring revascularisation because of angina or objective evidence of ischemia to CABG or percutaneous angioplasty (PTCA) [12]. There was no difference in 5 or 10-year survival when comparing patients treated with CABG or PTCA. In the subset of patients who had diabetes however, there was a survival benefit in patients who underwent CABG compared with those who had PTCA.

CKD population

Seventy-six (2.1%) of patients randomised in BARI had CKD defined as a serum creatinine of > 1.5mg/dL. These patients were examined in a sub-study analysis [13] and also compared with those in the study without CKD. Patients with CKD were older, more likely to be black, had more Diabetes Mellitus, CHF and hypertension as well as being more likely to have triple vessel disease and impaired LV function than those with normal renal function. Patients with CKD had a higher risk of all-cause and cardiac death at 7 years than those without CKD. Percutaneous angioplasty in patients with CKD was associated with a greater frequency of in-patient death, cardiogenic shock and combination of death and MI than patients without CKD. In patients who underwent surgery however, there was no difference in complications and death between the CKD and normal renal function group.

The Arterial Revascularisation Therapies Trial (ARTS) was a RCT comparing CABG and coronary stenting for the treatment of patients with multi-vessel CAD [14]. A post-hoc analysis [15] examined patients in this study with renal dysfunction defined as a creatinine clearance <60mL/min calculated using a CG formula. The mean creatinine clearance was 52mL/min. In both patients with creatinine clearances ≥ 60mL/min, there was no difference in mortality, cardiac death, MI, CVA or Q wave MI in comparing the CABG and the stent groups at 5 years. In both groups, the incidence of repeat revascularisation was greater in the stent arm compared with the CABG arm.

Revascularisation: stenting compared with angioplasty

Normal population

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, 2082 patients were randomised to PTCA ± abciximab versus stenting ± abciximab [16]. This study showed a reduction in re-stenosis in patients treated with stenting compared with angioplasty. Additional studies have also shown a reduction in the incidence of re-stenosis and target vessel revascularisation with stenting compared with angioplasty [17].

CKD population

A sub-study of CADILLAC [18] in patients with renal impairment defined as a creatinine clearance of less than or equal to 60ml/min as measured using the CG formula, examined 350 patients in this trial. The 30 day and 12-month mortality were markedly higher in patients with renal impairment compared with those with normal renal function. Severe re-stenosis and infarct artery re-occlusion were significantly higher in those with renal impairment. In addition, PTCA was associated with a higher rate of restenosis (26.5%) compared with stenting (15.1%; P = 0.15) with renal impairment. This difference was statistically significant in those without renal impairment.

Revascularisation: bare metal compared with drug eluting stents

Normal population

A meta-analysis has been undertaken examining 6 trials comparing sirolimus eluting stents with paclitaxel eluting stents [19] showing a significant reduction in the requirement for revascularisation in patients with sirolimus eluting stents. In addition, there was less re-stenosis in patients with sirolimus eluting stents than paclitaxel eluting stents. There was no difference in the rates of death, MI or stent thrombosis.

CKD population

The TAXUS-IV trial randomised patients with a creatinine less than 200mg/dL into either receiving the polymer-based slow-release paclitaxel-eluting stent or a bare metal stent [20]. A sub-group of the TAXUS-IV trial with renal impairment defined as creatinine clearance < 90mL/min calculated using the CG formula was undertaken [21]. Nearly 50% of patients in the trial had renal impairment (410 creatinine clearance 60 – 89mL/min, 223 creatinine clearance < 60mL/min). There was no difference in death, MI and stent thrombosis rate in patients with any renal function in patients treated with paclitaxel or bare metal stents. The paclitaxel stent did result in a reduction in the requirement for revascularisation in patients both with and without renal impairment and resulted in a lower re-stenosis rate. In the control arm (bare metal stent), renal dysfunction was independently associated with the risk of restenosis. In contrast, in the paclitaxel arm, renal function was not associated with re-stenosis

Effect of coronary artery bypass grafting on renal function

CKD population

There is one trial randomising patients with a MDRD calculated estimated glomerular filtration rate (eGFR) of <60mL/min undergoing primary coronary artery surgery to on-pump or off-pump groups [22]. Off-pump surgery was associated with a deterioration in renal function measured using both creatinine and glomerular filtration rate (GFR) compared with on-pump surgery. Three patients in the on-pump group compared with none in the off-pump group required haemodialysis.

Non randomised controlled studies

There are a number of studies examining revascularisation in patients with kidney disease. These include case reports, analyses of registry data, and case controlled studies.

Outcomes of coronary artery bypass grafting

Chronic kidney disease

There are a number of studies examining the outcomes of CABG in patients with CKD which is defined using a variety of methods (eGFR, creatinine clearance, serum creatinine). In comparison with the general population, patients with CKD are at increased risk of early [23,24,25] and late mortality [25,26,27,28,29] after CABG. Estimated GFR is an independent predictor of mortality in patients undergoing CABG (HR 0.80 per 10ml/min per 1.73m^2; 95% CI 0.72 – 0.89; P < 0.001) [30]. In addition, the presence of CKD is associated with increased morbidity and complications [31] compared with those with normal renal function.

Dialysis

Patients on dialysis have a greater perioperative mortality than those with normal renal function after CABG [32] and markedly reduced long-term survival compared with the general population [33]. Dialysis patients are also more likely to require blood transfusions than those with normal renal function [34]. There are two large studies of dialysis patients specifically examining revascularisation using registry data [35,36] Both studies show poor long term survival from CABG (2 year survival of 56%).

Transplant

There are few studies specifically examining CABG in transplant patients. One small study identified a 5-year survival of 85% and less than 10% of patients returning to haemodialysis after CABG [37]. The largest study [38] examining outcomes in 2661 renal transplant recipients found a 2-year survival of 82.7% after CABG with internal mammary artery grafting and a 67% 4-year survival.

Outcomes of percutaneous coronary intervention

Chronic Kidney Disease

CKD patients treated with PCI using angioplasty are at greater risk of in hospital [39,40], 30 day [41] and long term mortality [39,40,42,43,44] in addition to an increased risk of major cardiac events [44] and cardiac mortality [42] compared with those with normal renal function. Additionally, PCI in patients with CKD appears to be associated with a greater risk of re-stenosis and the requirement for target vessel revascularisation [39,41,45].

Dialysis

Similarly, patients on dialysis are at greater risk than the general population of 1 and 2-year mortality [42,45] and appear to be at high risk of re-stenosis [46,47].

Transplant

There are no studies specifically comparing the outcomes of transplant recipients after PCI with the general population. Survival at 4 years after PCI was 68.7% in a study including 652 renal transplant recipients [38]. Restenosis has not been examined in the current literature.

Outcomes of Coronary Artery Stenting

Chronic Kidney Disease

There are three moderate-sized studies examining the use of stents in populations of patients with CKD. The first examined the use of bare metal and drug eluting stents and compared the outcomes in patients with normal renal function defined as a creatinine clearance of >60mL/min with those with CKD (< 60mL/min). This study [48] found a greater incidence of mortality in the CKD group. In both patients with CKD and normal renal function, there was a reduction in re-stenosis with the use of drug eluting stents compared with bare metal stents. Another larger study [49] compared the use of drug eluting and bare metal stents with the normal and CKD populations. This study showed that CKD was an independent risk factor for target vessel revascularisation. In the overall group, there was an increased incidence of major cardiac adverse events and re-stenosis with the use of bare metal stents.

In comparison however, one study [50] examining outcomes with the normal and CKD populations, found no increase in the re-stenosis rate of patients treated with coronary stents compared with the

population with normal renal function, although CKD was an independent predictor of both death and myocardial infarction.

Dialysis

There is little in the literature reporting on the use of stents in dialysis patients and comparing outcomes with a matched group of patients with normal renal function. One study showed an increased incidence of re-stenosis in the dialysis group [48]. Another study, however, [45] reported no difference in the re-stenosis rate between the dialysis and normal renal function populations.

Transplant

There is one study examining the use of coronary artery stents using registry data [38]. In this study, 909 transplant recipients underwent CAS. Survival after stenting was 89.4% at 12 months and 72.6% at 4 years. Restenosis using stenst has not been specifically examined in the transplant population.

Comparisons of CABG and PCI (stable coronary artery disease)

Chronic kidney disease

There are few studies comparing outcomes of PCI and CABG in the CKD population. The largest study [51], examined data on over 58,000 patients with normal renal function (defined by a serum creatinine ≤ 2.5mg/dL) and compared outcomes after CABG or PCI in 840 patients with CKD >2,5mg/dL and 407 dialysis patients. While there was a survival advantage for CABG compared with PCI for dialysis patients, there was no significant benefit of CABG compared with PCI in terms of mortality in patients with CKD. Another study [52] examining outcomes in 750 patients with CKD and comparing those with normal renal function demonstrated poorer survival in those with CKD. Patients with CKD benefited from CABG compared with patients treated with no revascularisation, however there was no survival benefit of PCI compared with conservative treatment.

Dialysis

There are a number of studies comparing outcomes of percutaneous coronary intervention (PCI) and CABG in the dialysis population [36,40,51,52,53,54] in stable CAD. The smaller studies [53,54] show no difference in mortality between the use of CABG and PCI. The larger studies, however, show a reduced relative risk of all cause mortality for patients treated with CABG compared with PTCA [36,51] with the largest study [36] including 15784 patients on dialysis who underwent revascularisation demonstrating a reduced relative risk of all-cause death (RR 0.8, 95% CI: 0.76 - 0.84) and cardiac death (RR 0.77, 95% CI: 0.67 - 0.77) for CABG compared with PTCA and a reduction in all-cause death (RR 0.94, 95% CI: 0.88 - 0.99) and cardiac death (RR 0.92, 95% CI: 0.85 - 0.99) for CAS compared with PTCA. In diabetic patients, the benefit of CABG compared with PTCA was maintained and remained statistically significant, however, the stent outcomes were worse with no survival benefit of stenting compared with PTCA.

One study analysed the risk of MI [35] and demonstrated a significantly reduced incidence of MI in patients treated with CABG compared with PTCA.

There is a high risk of restenosis of coronary arteries in dialysis patients, and studies examining this showed a markedly higher incidence of target vessel revascularisation in patients treated with PTCA compared with CABG [53,54].

Transplant

A study of 2661 renal transplant recipients compared treatment with CABG, PTCA or stenting [38]. There was no difference in the relative risks of all-cause and cardiac deaths between the revascularisation groups, however, the relative risk of cardiac death or AMI was reduced in those treated with CABG using an internal mammary graft compared with PTCA (RR 0.57, 95% CI: 0.42 - 0.57)). A smaller study [55] showed no difference between CABG and PCI, however, this study examined only 83 patients.

Comparisons of CABG and PCI (unstable coronary artery disease)

Despite the high rate of cardiac events, there are only 2 studies examining interventional treatment in the renal populations with unstable CAD. In 640 dialysis patients with acute myocardial infarction, the rate of revascularisation was found to be low (7% PTCA, 5% CABG). Mortality of the whole group was 53% and revascularisation did not result in a difference in survival on a multivariate analysis. In a non-randomised observational study of 132 patients with acute MI and CKD, patients treated with thrombolysis had a survival benefit compared with patients who underwent acute PCI or no re-perfusion [56].

Comparisons of percutaneous angioplasty and coronary artery stenting

Chronic Kidney Disease

There are few studies comparing outcomes specifically between PTCA and stenting in the renal population. The largest study [57] examined a population of 1616 with CKD (predominantly CKD grade II) and compared outcomes with eras of high (94%) compared with low (18%) stent use. In this study, CAS was associated with fewer major adverse cardiac events, less repeat target vessel revascularisation and fewer myocardial infarctions than PTCA for all patients except those with a GFR of less than 29 mL/minute.

Dialysis

There are no large studies specifically comparing outcomes in the dialysis population. Case studies currently are insufficient to provide data in this area.

Transplantation

There are no large studies specifically comparing outcomes in the renal transplant population. Case studies currently are insufficient to provide data in this area.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

Suggestions for future research

Randomised controlled trials comparing different modalities of revascularization (eg CABG compared to Stenting) would assist with guiding decisions regarding the optimum mode of revascularization in patients with CKD.

Finally a RCT comparing conservative treatment with revascularization would assist with decision making regarding treatment of coronary artery disease in patients with CKD.

Conflict of interest

Helen Pilmore has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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Appendix

Figure 1. Trail profile for the FRISC II trial.

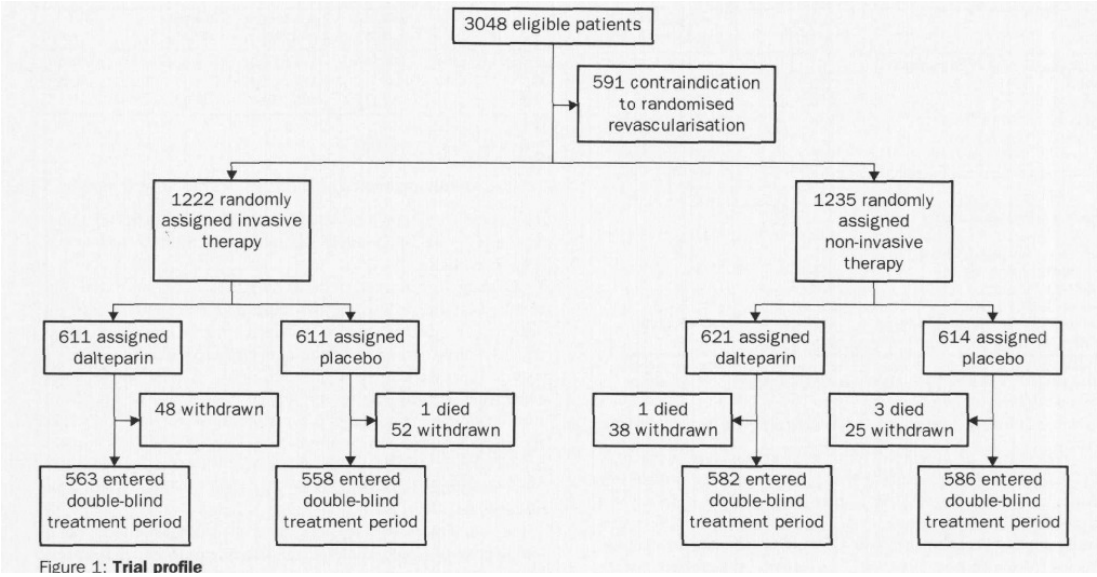

Figure 1: **Trial profile**

Source: FRISC II Investigators. Lancet 1999; 354: 708-15.